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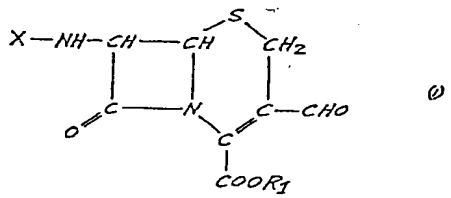
(19)

(54) PROCESS FOR THE MANUFACTURE OF CEPHALOSPORANIC ACID DERIVATIVES AND THE DERIVATIVES THUS OBTAINABLE

(71) We, CIBA-GEIGY AG, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a process for the manufacture of derivatives of cephalosporanic acid, namely 3 - desacetoxymethyl - 3 - formyl - 7 - amino - cephalosporanic acid (3 - formyl - 7 - amino - ceph - 3 - em-4 - carboxylic acid) and derivatives thereof, of the formula I

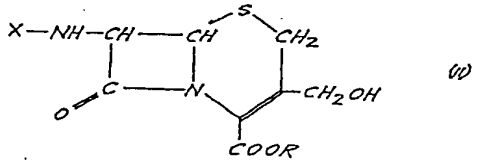


(I)

in which X represents a hydrogen atom or an acyl residue, and R_1 represents a hydrogen atom or a salt-forming cation or OR_1 represents a substituted methyl ester group capable of being split off by solvolysis, photolysis, enzymolysis or reduction.

In U.S. Patent No. 3,351,596 (which corresponds to U.K. Specification 1,211,018), is described for certain esters of the formula I and a process for their manufacture is characterised in that compounds that contain a hydroxymethyl group instead of the formyl group, are oxidised. As oxidising agents there are mentioned oxidising metal compounds such as oxidising metal oxides, for example, chromium trioxide or manganese dioxide. As esters there are mentioned, *inter alia*, lower alkyl esters and phenyl esters and also esters capable of being easily eliminated, such as benzyl, *p* - methoxy - benzyl, 3,5 - dimethoxybenzyl, diphenyl - methyl and C_1—C_6-halogen-alkyl esters. The term "lower" is used here and throughout the specification to denote groups having at most 5 carbon atoms. It has been found, however, that the above mentioned easily eliminable esters of 3-formyl compounds of the formula I cannot be obtained in adequate yields by the process described in the said patent because the halogenalkyl esters lactonize under the known conditions for their manufacture and the esters of the benzyl type, especially the benzhydryl esters, are attacked by the oxidising agent. Consequently, it is practically impossible to produce esters which can be converted into the free acid or salts thereof of the formula I by means of the patented process.

The present invention is based on the surprising observation that the oxidation of a splittable substituted methyl ester of a 3 - hydroxymethyl compound can be carried out with an aliphatic sulfoxide in the presence of an anhydride of a carboxylic acid, and that in this process neither the ester group nor the sulfide function of the cephalosporin ring system is attacked. The ester group can be split off by solvolysis, photolysis, hydrolysis or reduction. The invention provides a process for the manufacture of a compound of the formula I wherein a compound of the formula II



(II)

in which X has the meaning given above, and OR represents a substituted methyl ester group capable of being split off by solvolysis, enzymolysis, photolysis or reduction is oxidised with an aliphatic sulphoxide in the presence of an anhydride of a carboxylic acid, and, if desired, the ester group is split

[*Price 25p*]

off, and, if desired, a compound so obtained is converted into a salt or a salt so obtained is converted into the free acid or a different salt.

As aliphatic sulphoxides there may be mentioned more especially di-lower-alkyl sulphoxides, especially dimethyl sulphoxide, diethyl sulphoxide, dipropyl sulphoxide, dibutyl sulphoxide, and lower alkylene sulphoxides, for example, tetramethylene sulphoxide.

As anhydrides of carboxylic acids there are to be understood normal or mixed anhydrides of monobasic or dibasic aliphatic or aromatic carboxylic acids. There come into consideration primarily anhydrides of lower alkane carboxylic acids, for example, propionic anhydride, pivalic anhydride, succinic anhydride, benzoic anhydride, phthalic anhydride, but especially acetic anhydride.

The sulphoxide is advantageously used in excess and the anhydride is used in about the same molecular quantity as the sulphoxide. The sulphoxide and the anhydride may also be used as solvent. There may be used in addition an inert diluent, for example, benzene, toluene, or a mixture of inert solvents.

The oxidation can be carried out while cooling or with slight heating, for example, at a temperature within the range of about −50°C to +70°C. Preferably, room temperature is used.

The process of the invention can be used for the manufacture of a derivative of a compound of formula I having any acyl group at the 7-position. It should be noted that the oxidation according to the invention is not dependent on the kind of the acyl substituent X in 7-position of the cephalosporin ring system. X can therefore be any N^7-acyl residue known in the field of cephalosporins. If those acyl residues contain functional groups such as hydroxy, amino, carboxy or mercapto groups, it is advantageous to protect these groups temporarily during the reaction in known manner, especially by means of protective groups as they are known for protecting amino acids, for instance in the synthesis of peptides (cf. the Belgian Patent Specification No. 757,786). If desired, the protective groups can be split off from the resulting compounds of formula I, so that compounds of formula I having free functional groups are obtained. If the compound of formula I is to be converted into another antibiotically active cephalosporanic acid derivative, it may be of advantage to retain the protective groups until the reaction necessary to effect the conversion is finished and to split the protective group off after that reaction.

As acyl residues which are known in the cephalosporin field and which can be present in the compounds of formula I as substituent X, there may be used the acyl residues disclosed in the following patent specifications: U.S. Patent Specifications Nos. 3,218,318 (Flynn *et al.*, pubd. 16.11.1965), 3,236,841 (Kuehl *et al.*, pubd. 22.2.1966), 3,252,973 (Flynn *et al.*, pubd. 24.5.1966), 3,261,832 (Cowley *et al.*, pubd. 19.7.1966), 3,270,009 (Flynn et al., pubd. 30.8.1966), 3,351,596 (Chamberlin, pubd. 7.11.1967), 3,355,452 (Fechtig et al., pubd. 28.11.1967), 3,483,197 (Bickel *et al.*, pubd. 9.12.1969), or 3,484,437 (Urech *et al.*, pubd. 16.12.1969) or French Patent Specification 2,012,122 (Johnson *et al.*,).

Thus, the acyl residue is preferably the residue of a carboxylic or thiocarboxylic acid or a residue derived from carbonic acid, for example, a carbamic acid or monocarbonic acid ester residue. The carboxylic or thiocarboxylic acid residue may be derived from an unsubstituted or substituted aliphatic, cycloaliphatic, cycloaliphatic-aliphatic, araliphatic, heterocyclic or heterocyclic-aliphatic carboxylic acid.

In this regard, there may be mentioned

1) a residue of the formula

$$R_2(CH_2)_nCO,$$

in which n is 0 or an integer from 1 to 4, preferably 0 or 1, and the methylene group(s) is (are) optionally substituted, and R_2 is an unsubstituted or substituted (as mentioned below) aryl, cycloalkyl, heterocyclyl, aryloxy, arylthio, cycloalkoxy, heterocyclyloxy or heterocyclylthio residue. The aryl residues are monocyclic or bicyclic carbocyclic residues, especially phenyl residues. The cycloalkyl residues have 4—8 ring members, and are preferably cyclopentyl or cyclohexyl residues. The heterocyclyl residues are monocyclic or bicyclic residues with nitrogen, oxygen and/or sulphur as heteroatoms, especially residues with 1 to 4 heteroatoms and totally 5 or 6 ring atoms. The residues are unsaturated or partially or fully saturated; they can contains a condensed benzene ring. As examples there may be mentioned furyl, thienyl, pyrryl, cumaryl, thiocumaryl, indolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiadiazolyl, oxadiazolyl thiatriazolyl, pyranyl, pyridyl, quinolyl, pyrimidyl, pyrazinyl, thiazinyl, dithiazinyl, thiadiazinyl, triazinyl, and tetrazinyl residues, optionally also their isomers and their products of hydrogenation. As substituents of the rings there may be mentioned, above all, lower alkyl or lower alkoxy groups, or lower carbalkoxy groups, these groups having at most 5 carbon atoms, for example methyl, ethyl, propyl, butyl, pentyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, tert. butyloxycarbonyl, and tert. amyloxycarbonyl groups; halogen atoms, for example, bromine, iodine, fluorine and chlorine atoms and the

pseudohalogen trifluormethyl group, a nitro, formyl, cyano or carboxycarbonyl group; a hydroxy, amino, carboxy or mercapto group which group may be free or protected by protective groups, for instance those enumerated in the above mentioned Belgian Patent Specification No. 757,786, also a phenyl group which may be unsubstituted or substituted by any one or more of the substituents mentioned above. The methylene group(s) of the acyl radical may be substituted by any of the substituents mentioned above with the exception of the lower alkyl group. As examples of acyl residues of the formula

$$R_2(CH_2)_nCO$$

there may be mentioned 2,6 - dimethoxybenzoyl, tetrahydronaphthoyl, 2 - methoxynaphthoyl, 2 - ethoxy - naphthoyl, cyclopentanoyl, 2 - phenyl - 5 - methylisoxazolyl - carbonyl, 2 - (2' - chlorphenyl) - 5 - methyl - isoxazolyl - carbonyl, phenylacetyl, thienyl(2) - acetyl, thienyl(3) - acetyl, furyl(2) - acetyl, S - phenylthioacetyl, phenoxyacetyl, S - bromophenylthioacetyl, α - phenoxypropionyl, α - phenoxy - phenylacetyl, α - methoxy - phenylacetyl, α - methoxy - 3,4 - dichlor - phenylacetyl, S - benzylthioacetyl, S - benzylthiopropionyl, pyridyl(2) - thioacetyl, tetrazolyl(5) - acetyl, tetrazolyl(1) - acetyl, imidazolyl(2) - acetyl, imidazolyl(1) - acetyl, imidazolyl(2) - thioacetyl, 1,3,4 - thiadiazolyl(2) - thioacetyl, thiazolyl(2) - thioacetyl, 1,2,4 - triazolyl(3) - thioacetyl, 5 - mercapto - 1,3,4 - thiadiazolyl(2) - thioacetyl, 5 - amino - tetrazolyl(1) - acetyl, α - amino - α - phenyl - acetyl, α - cyan - α - phenyl - acetyl, α - hydroxy - α - phenyl - acetyl, α - carboxy - α - phenylacetyl, α - methoxy - α - phenyl - acetyl, α - azido - α - phenyl - acetyl, α - formylamino - α - phenyl - acetyl, α - (2,2,2 - trichlorethyloxycarbonylamino) - α - phenylacetyl, α - (tert.butyloxycarbonylamino) - α - phenyl - acetyl, α - (2 - iodethoxycarbonyl) - α - phenyl - acetyl, α - (2 - bromethoxycarbonyl) - α - phenyl - acetyl, and α - (2 - diphenyl - 2 - propyloxycarbonyl) - α - phenyl - acetyl residues, as well as corresponding p - hydroxyphenyl - acetyl, p - chlorphenyl - acetyl, cyclohexyl - acetyl, thienyl(2) - acetyl, thienyl(3) - acetyl and furyl(2) - acetyl residues which have in the α-position the substituents indicated for the phenyl - acetyl residues.

As acyl residue X there may further be mentioned

2) a residue of the formula

$$C_nH_{2n+1}CO$$

or

$$C_nH_{2n-1}CO,$$

in which n is an integer of from 1 to 7, and the chain is straight or branched and may be interrupted by an oxygen or sulphur atom or substituted by one or more substituents selected from the substituents indicated under 1) for the cyclic residues, with the exception of the lower alkyl residues, and azido and ureido groups. Examples of acyl residues of this kind are: acetyl, propionyl, butyryl, valeryl, hexanoyl, heptanoyl, octanoyl, vinyl - acrylyl, crotonyl, 2 - pentenoyl, butylthioacetyl, allylthioacetyl, chloracetyl, bromacetyl, dichloracetyl, dibromacetyl, diidoacetyl, difluoracetyl, trifluoracetyl, β - brompropionyl, cyanacetyl, β - cyanpropionyl, δ - amino - δ - carboxy - valeryl, δ - phthaloylamino - δ - carboxy - valeryl, δ - ethoxycarbonylamino - δ - carboxy - valeryl, δ - isobutyl - oxycarbonylamino - δ - carboxyvaleryl, δ - benzyloxycarbonylamino - δ - carboxy - valeryl, δ - ethylaminocarbonylamino - δ - carboxy - valeryl, δ - (n - butyl)-aminocarbonylamino - δ - carboxy - valeryl, δ - (tert.butyloxycarbonylamino) - δ - carboxy - valeryl, δ - (2,2,2 - trichlorethyloxycarbonylamino) - δ - carboxy - valeryl, δ - (2 - biphenylyl - 2 - propyloxycarbonyl)-δ - carboxy - valeryl, δ - (2 - iodethoxycarbonyl) - δ - carboxy - valeryl, δ - (α - chloracetyl) - amino - δ - carboxy - valeryl, δ - (α,α dichloracetyl) - amino - δ - carboxyvaleryl, δ - benzoylamino - δ - carboxyvaleryl, δ - trinitrophenylamino - δ - carboxyvaleryl, α - azido - acetyl, α - methoxycarbonyl - acetyl, α - ethoxycarbonyl - acetyl, α,α - dimethoxycarbonyl - acetyl, α,α - diethoxycarbonyl - acetyl and α - cyan - β - dimethylacrylyl residues.

The acyl residue X may also be

3) a residue of the formula

$$R_3—NH—CO$$

in which R_3 is an unsubstituted or substituted aromatic, araliphatic or aliphatic hydrocarbon residue, preferably an unsubstituted or substituted lower alkyl residue. The substituents of the aromatic residues are those mentioned under 1) for the cyclic residues, and the substituents of the aliphatic residues are the same, with the exception of the lower alkyl residues. Examples of acyl residues of this kind are: methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, tert. butylcarbamoyl, phenylcarbamoyl, p - chlorphenyl - carbamoyl, benzylcarbamoyl, β - chlorethylcarbamoyl, 1,1 - dimethyl - 2 - chlorethylcarbamoyl, and 2 - brompropylcarbamoyl residues.

The acyl residue X may further be

4) a residue of the formula

$$R_4—O—CO$$

in which R_4 has the same meaning as R_3

under 3) above. Examples of acyl residues of this kind are: methyloxycarbonyl, ethyloxycarbonyl, propyloxycarbonyl, tert.butyloxycarbonyl, tert. - amyloxycarbonyl, allyloxycarbonyl, cyclopentyloxycarbonyl, cyclohexyloxycarbonyl, adamantyloxycarbonyl, tolyloxycarbonyl, benzyloxycarbonyl, *p* - methoxybenzyloxycarbonyl, and 2 - (*p* - biphenylyl)-2 - propyloxycarbonyl residues.

Especially preferred acyl residues X are phenylacetyl, phenoxyacetyl, phenylglycyl, thienyl(2) - acetyl, thienyl(3) - acetyl, furyl-(2) - acetyl, tetrazolyl(1) - acetyl, methoxycarbonyl - acetyl, ethoxycarbonyl - acetyl, cyanacetyl and ω - amino - adipoyl residues which residues may be unsubstituted or substituted as described above.

The substituted methyl ester group OR or OR_1 capable of being split off by solvolysis, enzymolysis, photolysis or reduction from the compounds of the formulae I or II preferably contains substituents which cause the ester to be sterically hindered, and which, furthermore, are known in the cephalosporin field as facilitating the removal of the methyl ester group, for instance by solvolysis, reduction, photolysis or enzymatically (for instance on oral administration cf., German Patent Specification No. 1,904,585 or U.S. Patent Specification No. 3,488,729). The methyl ester group can contain one or more substituents. The substituents are preferably unsubstituted or substituted by mono- or bicyclic aryl or aryloxy residues for example, an unsubstituted or substituted naphthyl, benzoyl or above all phenyl residue, further lower alkanoyloxy groups with at most 5 carbon atoms and substituted or substituted aroyloxy groups. Substituents of the aryl, aroyl or aroyloxy residues are those which are mentioned under 1) above for cyclic residues, especially one or more nitro groups and/or halogen atoms, for example, fluorine, bromine, iodine and especially chlorine, and/or lower alkyl and/or lower alkoxy groups such as methyl, ethyl, propyl, ethoxy, propoxy, especially methoxy. The substituted methyl group is therefore, for example, phenacyl, bromphenacyl, acetoxymethyl, pivaloyloxymethyl, benzoyloxymethyl, benzyl, *p* - methoxybenzyl, 3,5 - dimethoxybenzyl, 3,4 - dimethoxybenzyl, *p* - nitrobenzyl, 2,4,6 - trimethylbenzyl, diphenylmethyl, di - (*p* - methoxyphenyl) - methyl, α - phenyl - α - (3,4 - dimethoxy - 6 - nitro - phenyl) - methyl, α - methyl - α - (3,4 - dimethoxy - 6 - nitro - phenyl)-methyl or triphenylmethyl group.

The above mentioned ester groups can be split off in known manner after the oxidation according to the invention, or, if desired, after converting the product of formula I into another product, as has been mentioned above. The ester group can, for example, be split off by reduction, for instance with nascent or catalytically activated hydrogen, or by photolysis or by solvolysis, especially hydrolysis in an acid medium (trifluoracetic acid, formic acid, acetic acid, hydrochloric acid) or in a weakly alkaline medium (up to a pH of about 10).

Salts of compounds of the formula I, in which X is an acyl residue, are metal salts, preferably physiologically tolerable alkali metal or alkaline earth metal salts, for example sodium, potassium, ammonium or calcium salts or salts with organic bases, for example, triethylamine, N - ethylpiperidine, dibenzylethylene diamine, procaine, di - isopropylamine, or ethanolamine. When X is basic, internal salts may be formed. The salts can be obtained in known manner, for example, by treatment with bases, if desired, with the use of ion-exchangers.

Owing to the close relationship between the compounds of the invention in the free form and in the form of salts thereof, it is to be understood that in the foregoing and succeeding description references to the free compounds and salts include, where the context permits, also the corresponding salts or free compounds.

The compounds of the formula II used as starting materials are known or can be made by methods in themselves known. For example they can be obtained from compounds of the formula II, in which R represents hydrogen, by esterification with a diazomethane substituted as mentioned above for methanol, or by reacting a compound of the formula II, in which R represents an alkali metal or alkaline earth metal ion or an ammonium ion, for example, triethylammonium, with a reactive ester, for example, a halide, especially a chloride, bromide or iodine, of a methanol substituted as mentioned above, for example, by reaction of a compound of the formula II, in which R is sodium, with phenacyl bromide. The production of the compound of the formula II, in which X and R represent a hydrogen atom, (O - desacetyl - 7 - amino-cephalosporanic acid) can be carried out, for example, by the process described in British Patent Specification No. 1,080,904 by desacetylating 7 - amino - cephalosporanic acid with acetylesterase obtained from *Bacillus subtilis*. A compound of the formula II, in which X is an acyl residue and R is hydrogen, can be made by desacetylating the corresponding 7 - acylamino - cephalosporanic acid by the process of the aforesaid British Specification.

The compounds of the formula I possess an antibacterial action, for example, against penicillin - sensitive and penicillin - resistant *Staphyloccucus aureus, Klebsiella pneumoniae* and *Salmonella typhosa*. This applies especially to the salts. They can therefore be used for combating infections, which are caused by such micro-organisms, and also as additions to foodstuffs, for preserving nutrients or as disin-

fecting agents. The compounds of the formula I are also useful as intermediate products for making further derivatives of 7 - amino-cephalosporanic acid.

The compounds of the invention are useful as medicaments, for example, in the form of pharmaceutical preparations. These preparations contain the compounds in admixture or conjunction with a pharmaceutically suitable organic or inorganic, solid or liquid carrier material, and are preferably in a form suitable for enteral, topical or parenteral administration. As carrier materials there are used substances that do not react with the compounds of the invention, for example, water, gelatine, lactose, starches, stearyl alcohol, magnesium stearate, talc, vegetable oils, benzyl alcohols, gums, propylene glycol, polyalkylene glycols, white petroleum jelly, cholesterol or other known carrier for medicaments. The pharmaceutical preparations may be, for example, in the form of tablets, dragées, salves, creams, capsules or, in liquid form, as solutions, suspensions or emulsions. If desired, they may be sterilised and/or may contain assistants, for example, preserving, stabilising, wetting or emulsifying agents, solution promoters or salts for regulating the osmotic pressure or buffers. They may also contain other pharmaceutically useful substances. The preparations are made up by the usual methods.

The following Examples illustrate the invention:

EXAMPLE 1

0.2 gram (0.39 mMol) of diphenylmethyl-3 - hydroxymethyl - 7 - phenylacetylamino-ceph - 3 - em - 4 - oate is dissolved in 5 ml of absolute dimethyl sulphoxide and 5 ml of acetic anhydride, and the whole is allowed to stand in the dark at room temperature for 5 hours. The greenish brown reaction solution is evaporated to dryness in a high vacuum, toluene is added to the residue, and the solution is evaporated to dryness. The crude product is taken up in methylene chloride and washed with a solution of sodium chloride. The organic phase is dried over magnesium sulphate and the solution is evaporated *in vacuo*.

The residue (0.2 gram) is chromatographed on a column of 10 grams of silica gel (MERCK, Trade Mark, puriss., with the addition of 5% of water). Diphenylmethyl - 3 - formyl - 7 - phenylacetylamino - ceph - 3 - em - 4 - oate is eluted with methylene chloride (0.145 gram). Fractions 2 and 3, which are unitary according to thin layer chromatography, are dissolved in methylene chloride and cyclohexane is added, while heating, whereby a gelatinised precipitate forms. The latter is filtered off, washed with ether+pentane and dried on the suction filter. The pale yellow powder so obtained melts at 123—125°C (uncorrected). For the purpose of analysis the product is dried in a high vacuum for 20 hours at room temperature. According to the nuclear resonance spectrum it still contains about one fifth mol of cyclohexane. Infra-red spectrum in CH_2Cl_2, *inter alia* 2.90; 3.39; 5.54; 5.77; 5.91 (shoulder); 5.97; 6.22; 6.68; 7.28; 8.16 μ.

Infra-red spectrum in Nujol (Trade Mark) *inter alia*, 3.02; 55.54; 5.77; 5.89; 6.02; 6.23; 6.50; 8.02 μ.

In the ultra-violet spectrum (in rectified spirit) $\lambda_{max.}$=310 nm (ε=9'250), λ_{min}=255 nm (ε=4'950).

In the proton resonance spectrum in $CDCl_3$ (100 Mc):

		Association.
$-\delta$=3.17 } [2H]	AB-spectrum.	—CH_2—S—
=3.88 }	J_{AB}=18.5 cps	
=3.57 [2H]	(s)	—CH_2—CO—
=4.94 [1H]	(d) J=5 cps	H—6
=5.91 [1H]	(dd) J=5, J'=9cps	$CH(C_6H_5)_2$
=6.29 [1H]	(d) J'=9 cps	H—7
=7.02 [1H]	(s)	—NH—CO—
=7.25 }	(s)	
} [15H]	(s)	—3—C_6H_5
=7.31 }	(s)	
=9.60 [1H]	(s)	—CHO

In the thin layer chromatogram on silica gel G the Rf-value=0.75 in the solvent system ethyl acetate/toluene (1:1). (Development with iodine vapour or detection with UV_{254}).

0.110 gram of diphenylmethyl - 3 - formyl-7 - phenylacetyl - amino - ceph - 3 - em-4 - oate (which according to the NMR-spectrum contains about 0.2 mol of cyclohexane) is covered with a mixture of 1 ml of anisole and 4 ml of absolute trifluoracetic acid and allowed to stand for 20 minutes at room temperature. The reaction solution is then evaporated to dryness in a high vacuum with the repeated addition of absolute toluene. The residue is distributed between 10 ml of ether and 10 ml of an 0.5-mol solution of dipotassium hydrogen phosphate. The ethereal phase is washed with a solution of dipotassium hydrogen phosphate and discarded. The dipotassium hydrogen phosphate extract, which

contains the potassium salt of 3 - formyl - 7 - phenylacetylamino - ceph - 3 - em - 4 - carboxylic acid, is acidified with dilute phosphoric acid to a pH-value of 2, and is extracted first with 50 ml of ethyl acetate and then twice with 20 ml of ethyl acetate on each occasion, and is discarded. The ethyl acetate extracts are washed with sodium chloride solution, dried over sodium sulphate, and freed from solvent *in vacuo*, whereby the acid is obtained in the form of a yellowish product (66 mg).

The ultra-violet spectrum of the substance in rectified spirit shows an absorption maximum at 289 nm and a minimum at 244 nm.

The infra-red spectrum of the acid or of the lactol in equilibrium therewith (in tetrahydrofuran) shows, *inter alia*, absorption bands at 2.91 (shoulder); 3.10; 3.85 (shoulder) 4.25 (shoulder); 5.65; 5.75; 5.94; 6.25 and 6.62 μ.

The starting material can be prepared as follows:

11.82 grams of the sodium salt of crude O - desacetyl - 7 - phenylacetylamino - cephalosporanic acid (produced by enzymatic desaceylation of the sodium salt of 7 - phenylacetylamino-cephthalosporanic acid by means of a purified enzyme extract of *Bac. subtilis*, strain ATCC 6633, followed by lyophilisation of the reaction solution) are dissolved in 200 ml of water. The solution is covered with 400 ml of ethyl acetate and acidified with phosphoric acid to a pH-value of 2. The aqueous phase is separated and extracted twice with 150 ml of ethyl acetate on each occasion. The organic extracts are washed four times with 50 ml of water on each occasion, and dried over magnesium sulphate. The solution is then concentrated to a volume of about 400 ml, and an excess of diphenyl - diazomethane solution is added. The whole is allowed to stand at room temperature for 3 hours, and the precipitated granular crystals are filtered off. The filtrate is concentrated to about 200 ml, cyclohexane is added while heating, and, after the mixture has cooled to room temperature, it is inserted in a cooling cabinet. The precipitated material is filtered off with suction, washed and dried (6.3 grams).

After being recrystallised from a mixture of acetone and cyclohexane, the purified product melts at 176—176.5°C (uncorrected).

$[\alpha]_D^{20} = -6° \pm 1°$ (c=1.231% in chloroform).

In the thin layer chromatogram on silica gel G:

Rf=0.27 in chloroform-acetone (4:1);
Rf=0.20 in toluene-acetone (3:1);
Rf=0.53 in methylene chloride-acetone (6:1).

(Detected with iodine vapour or UV_{254}).

EXAMPLE 2

0.50 Gram of diphenylmethyl - 3 - hydroxymethyl - 7β - [N' - tert. - butyloxycarbonyl-D - (α) - phenylglycylamino] - ceph - 3 - em - 4 - oate are dissaolved in 2.5 ml of absolute dimethylsulphoxide and 2.5 ml of acetic anhydride. The colourless solution is left to stand for 5 hours at room temperature in the dark, and the golden yellow reaction mixture is then concentrated to dryness in a high vacuum. The residue is poured onto a column of silica gel (45 g; MERCK puriss). Elution is carried out initially with methylene chloride; fractions of 50 ml each are collected. Fractions 1—3 contain 31 mg of non-polar impurities, which are discarded. Diphenylmethyl - 3 - formyl - 7β - [N' - tert. - butyloxycarbonyl - D - (α) - phenylglycylamino] - ceph - 3 - em - 4 - oate (0.28 g), which is pure according to thin-layer chromatography, is eluted from fractions 4—5 (likewise elution with methylene chloride) and 6—8 (elution with methylene chloride+2% methyl acetate). By using increasing concentrations of methyl acetate, still further, though impure, product can be obtained.

In thin-layer chromatogram on silica gel, the product has the following Rf values (detection with iodine vapour or $UV_{254\ nm}$):

in the system toluene-acetone (4:1) Rf=0.74 (starting material: 0.26)
in the system toluene-acetone (2:1) Rf=0.88 (starting material: 0.44)
in the system toluene-ethyl acetate (1:1) Rf=0.93 (starting material: 0.30).

Melting point=178—180°C (with decomposition).

In UV spectrum in methylene chloride:

λ_{max}=292 nm (ε=13,900)
λ_{min}=242 nm (ε=3,500).

The IR spectrum in methylene chloride shows bands at 2.92; 5.54; 5.78; 5.88; 5.97; 6.22; 6.68; 7.28; 8.15; 8.59; 9.14; 9.49; 9.98; 11.58 μ.

The starting material can be manufactured as follows:

4.0 Grams of 3 - acetoxymethyl - 7β - [N' - tert. - butyloxycarbonyl - D - (α) - phenylglycylamino] - ceph - 3 - em - 4 - carboxylic acid are suspended in 50 ml of water. After addition of 7.7 ml of N sodium hydroxide solution a clear solution is obtained, which is treated with 0.1 g of purified esterase from *Bact. subtilis*, strain ATCC 6633 (cf. British Patent 1,080,904). The reaction solution is stirred at 35°C and the pH maintained at 7.3 by adding 0.5N sodium hydroxide solution. The reaction is completed (5 hours)

after 14.4 ml of 0.5N sodium hydroxide solution have been consumed.

The reaction solution is adjusted to pH 6.5, clarified with activated charcoal, then covered with approx. 120 ml of ethyl acetate and acidified while stirring with 5M phosphoric acid to pH 2.2. The solution is cooled with ice, saturated with sodium chloride and the phases are separated. The aqueous layer is re-extracted with 2×100 ml of ethyl acetate and discarded. The organic extracts are washed with 4×30 ml of saturated sodium chloride solution and dried briefly over anhydrous magnesium sulphate. After filtration, the solution of the 3 - hydroxymethyl - 7β - [N' - tert. - butyloxycarbonyl - D - (α) - phenylglycylamino] - ceph - 3 - em - 4 - carboxylic acid is treated with diphenyldiazomethane in cyclohexane and left to stand for 45 minutes at room temperature. The still faintly reddish coloured solution is concentrated to approx. 200 ml, the concentrate treated with ether and left to stand overnight in a cooling cabinet. The colourless crystalline product that has settled out in the process is filtered off and washed with ether while cooling. After drying in a vacuum desiccator, crystals (2.975 g) of diphenylmethyl - 3 - formyl - 7β - [N' - tert.butyloxycarbonyl-D - (α) - phenylglycylamino] - ceph - 3 - em - 4 - oate are obtained, which decompose at 128°C. The mother solution, which is concentrated by evaporation, contains further product, which can be isolated by column chromatography on silica gel (MERCK puriss.).

EXAMPLE 3

By proceeding in a manner analogous to that described in Example 2, diphenylmethyl-3 - hydroxymethyl - 7β - [N' - tert. - butyloxycarbonyl - D - (α) - phenylglycylamino] - ceph - 3 - em - 4 - oate is treated with di(*n*-butyl) - sulphoxide (redistilled) and acetic anhydride.

The reaction mixture is concentrated in a high vacuum and the residue is taken up in ether and water. The layers are separated and the ether phase extracted repeatedly with water. The aqueous phases are re-extracted with 2 portions of water and discarded. The combined organic extracts are dried over magnesium sulphate and freed from solvent in vacuo. The residue is purified by column chromatography on silica gel as described in Example 2. The same product as in Example 2 is obtained.

EXAMPLE 4

0.77 Gram of diphenylmethyl - 3 - hydroxymethyl - 7β - [5' - phthalimido - 5' - diphenylmethyloxycarbonyl - *n* - valeroylamino] - ceph - 3 - em - 4 - oate are dissolved in 15 ml of absolute dimethylformamide and 15 ml of acetic anhydride. The faintly yellow coloured solution is kept in the dark for 6 hours at room temperature.

The brownish yellow reaction mixture is evaporated to dryness in vacuo while adding absolute toluene. The residue is purified by chromatography on 50 times its weight of silica gel (MERCK puriss.). The diphenylmethyl - 3 - formyl - 7β - [5' - phthalimido - 5' - diphenylmethoxycarbonyl - *n* - valeroyl - amino] - ceph - 3 - em - 4 - oate which is pure according to thin-layer chromatography is eluted with methylene chloride + 2—3% of methyl acetate. The unitary fractions are combined and lyophilised from dioxane.

The IR spectrum of the amorphous compound, which is dried in a high vacuum, shows i.a. the following absorption bands in methylene chloride: 2.90; 5.55; 5.62; 5.74; 5.81; 5.89; 5.93; 6.23; 6.68, 7.20; 8.16; 8.47; 9.15 μ.

In thin-layer chromatagram on silica gel, the product has the following Rf values (detection with iodine vapour or $UV_{254\ nm}$):

in the system toluene-acetone (4:1)
Rf=0.63 (starting material: 0.20)
in the system toluene-acetone (2:1)
Rf=0.84 (starting material: 0.38)
in the system toluene-ethyl acetate (1:1)
Rf=0.82 (starting material: 0.17).

EXAMPLE 5

A solution of 1.03 g diphenylmethyl - 3 - hydroxymethyl - 7β - phenylacetylamino-ceph - 3 - em - 4 - oate in 10 ml of absolute dimethylsulphoxide and 6 ml of melted benzoic anhydride is kept in the dark for 16 hours at room temperature. The reaction solution is evaporated in a high vacuum. The residue is taken up in methylene chloride and shaken out repeatedly with 0.5M dipotassium hydrogen phosphate solution. The organic phase is then washed with water, dried over magnesium sulphate and freed from solvent *in vacuo*.

The crude product is chromatographed on 50 g of silica gel (MERCK puriss., deactivated with 5% water). The diphenylmethyl-3 - formyl - 7β - phenylacetylamino - ceph-3 - em - 4 - oate is eluted firstly with methylene chloride and then with methylene chloride + 1% of methyl acetate. The fractions, which are unitary according to thin-layer chromatography, are combined and crystallised from benzene-cyclohexane. The faintly yellow crystals of the product are dried for 48 hours at 50°C in a high vacuum in order to completely remove the solvent. The resulting product melts at 124—125°C (uncorrected). The optical rotation $[\alpha]_D^{20} = -95.5° \pm 2°$ (c=0.207 in dioxane).

EXAMPLE 6

Proceeding in a manner analogous to that described in Example 5, 1.03 grams of di-

phenylmethyl - 3 - hydroxy - methyl - 7β - phenylacetylamino - ceph - 3 - em - 4 - oate are reacted overnight at room temperature with 10 ml of tetramethylsulphoxide and 5 ml of acetic anhydride.

The reaction mixture is then evaporated in a high vacuum and the residue taken up in ether and water. The aqueous phase is separated, re-extracted with ether and discarded. The ether extracts are dried over magnesium sulphate after being repeatedly washed with water, and freed from solvent *in vacuo*.

As in Example 5, the crude diphenylmethyl-3 - formyl - 7β - phenylacetylamino - ceph-3 - em - 4 - oate is separated from some more polar impurities by means of column chromatography on silica gel (deactivated by addition of 5% water) and crystallised from benzene-cyclohexane.

EXAMPLE 7

By proceeding in a manner analogous to Example 1, 0.50 grams of diphenylmethyl-3 - hydroxymethyl - 7β - (2′ - thienylacetylamino) - ceph - 3 - em - 4 - oate are dissolved in 10 ml of absolute dimethylsulphoxide and 10 ml of acetic anhydride and the reaction mixture is worked up after a 5 hour reaction period. The diphenylmethyl - 3 - formyl - 7β - (2′ - thienylacetylamino)-ceph - 3 - em - 4 - oate is purified by column chromatography on silica gel (MERCK puriss. addition of 5% water, elution with methylene chloride+3% methyl acetate. In thin-layer chromatogram on silica gel G plates in the system toluene-ethyl acetate (1:1), the product has an Rf value of 0.72 (detection with iodine vapour or $UV_{254\ nm}$).

The starting material is manufactured by reacting 1.0 g of 3 - hydroxymethyl - 7β - (2′ - thienylacetylamino) - ceph - 3 - em - 4 - carboxylic acid with 0.7 g of diphenyldiazomethane in tetrahydrofuran for 3 hours at room temperature. The crude product, which is obtained after evaporating off the solvent, is dissolved in ethyl acetate and washed with 0.5 M dipotassium hydrogen phosphate solution and washed with saturated sodium chloride solution. After the solution has been dried over anhydrous magnesium sulphate, it is freed from solvent at reduced pressure and the foamy crude product (1.08 g) is crystallised from methanol. Melting point: 164—165°C (uncorr.); optical rotation $[\alpha]_D^{20} = +24° \pm 1°$ (c=0.985 in dioxane).

EXAMPLE 8

A solution of 0.95 g bis - (4 - methoxyphenyl) - methyl - 3 - hydroxymethyl - 7β - phenylacetylamino - ceph - 3 - em - 4 - oate in 10 ml of absolute dimethylsulphoxide and 10 ml of acetic anhydride is left to stand in the dark for 4 hours at room temperature. The yellowish brown reaction solution is evaporated to dryness in a high vacuum at 30°C bath temperature. The residue is partitioned repeatedly between methylene chloride and water. The product (0.93 g) that is obtained on evaporation of the organic phase is chromatographed on 50 times its weight of silica gel (MERCK puriss., addition of 7% water). The bis - (4 - methoxyphenyl) - methyl - 3 - formyl - 7β - phenylacetylamino - ceph - 3 - em - 4 - oate is eluted with methylene chloride. The fractions (0.55 g) which are unitary according to thin-layer chromatography are lyophilised from dioxane. In thin-layer chromatogram on silica gel in the system glacial acetic acid-toluene (1:1), the product has an Rf value of 0.73.

The starting material is manufactured as follows. 3.48 Grams of 3 - hydroxymethyl-7β - phenylacetylamino - ceph - 3 - em - 4 - carboxylic acid crystallised from ethyl acetate (m.p. 139—140°C, UV absorption in 0.1N sodium bicarbonate solution: 260 nm, ε=(8.050) are dissolved in dioxane/methanol (4:1) v/v) and treated portionwise over the course of 90 minutes with 2.5 g of bis - (4 - methoxyphenyl) - diazomethane [decomposition point 112—113°C, prepared by oxidation of 4,4′ - dimethoxy - benzophenonehydrazone with activated manganese dioxide in methylene chloride and crystallised at low temperature from a small amount of methylene chloride and ether]. The reaction solution is carefully freed from solvent in vacuo and taken up in ethyl acetate. Extraction is carried out successively with 0.5 M dipotassium hydrogen phosphate and water and the extract dried over magnesium sulphate. After filtration, the solution is concentrated and the residue treated with ether while heating. The fine precipitate is filtered off and dried *in vacuo* at room temperature.

EXAMPLE 9

By proceeding in a manner analogous to Example 8, (phenyl - α - naphthyl) - methyl-3 - formyl - 7β - phenylacetylamino - ceph-3 - em - 4 - oate is manufactured by reacting 0.6 g of (phenyl - α - naphthyl) - methyl-3 - hydroxymethyl - 7β - phenylacetylamino-ceph - 3 - em - 4 - oate with 8 ml of absolute dimethylsulphoxide and 8 ml of acetic anhydride, and isolated.

The starting material is obtained by esterifying 3 - hydroxymethyl - 7β - phenylacetylamino - ceph - 3 - em - 4 - carboxylic acid with phenyl - α - naphthyl - diazomethane (decomp. pt. 80°C, preparation according to H. Reimlinger, Chem. Ber. *97*, 3498 (1964)) in absolute tetrahydrofuran.

EXAMPLE 10

By proceeding in a manner analogous to Example 1, benzyl - 3 - formyl - 7β - phenylacetylamino 1 ceph - 3 - em - 4 - oate is prepared from benzyl - 3 - hydroxymethyl-

7β - phenylacetylamino - ceph - 3 - em - 4 - oate in 10 ml of absolute dimethylsulphoxide and 10 ml of acetic anhydride and worked up. The crude product is chromatographed on 50 times its weight of silica gel (MERCK puriss., addition of 5% water). The product is eluted with methylene chloride and lyophilised from dioxane. Desacetyl - 7 - phenylacetamino - cephalosporanic acid lactone, which constitutes the principal impurity, is eluted with methylene chloride/methyl acetate (4:1) and (1:1).

The starting material is manufactured as follows:

3.48 Grams of 3 - hydroxymethyl - 7β - phenylacetylamino - ceph - 3 - em - 4 - carboxylic acid are dissolved in absolute tetrahydrofuran, treated with excess phenyldiazomethane in ether and left to stand for 2 hours at room temperature. After addition of a few drops of ethyl acetate, the reaction solution is evaporated to dryness *in vacuo*. The residue is taken up in ethyl acetate, washed with 0.5 M dipotassium hydrogenphosphate solution and water and dried over magnesium sulphate. The filtered solution is concentrated and treated with cyclohexane while heating, in the process of which a white precipitate settles out which is filtered off and dried in vacuo at room temperature. The product begins to sinter at 125°C and melts indistinctly between 130 and 135°C. It is used for the oxidation reaction without further purification.

EXAMPLE 11

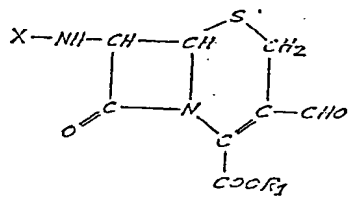
A solution of 1.03 g of diphenylmethyl-3 - hydroxymethyl - 7β - phenylacetylamino-ceph - 3 - em - 4 - oate in 12 ml of absolute dimethylsulphoxide is treated with 12 ml of pivalic anhydride and left to stand in the dark for 20 hours at room temperature. The yellowish brown reaction mixture is evaporated to dryness in vacuo. The residue is taken up in methylene chloride, washed with 0.5 dipotassium hydrogen phosphate solution and water and dried over magnesium sulphate. After the solvent has been evaporated off, 1.05 g of crude product are obtained, which is purified by column chromatography as in Example 1. The resulting diphenyl - 3 - formyl - 7β - phenylacetylamino - ceph - 3 - em - 4 - oate is identical with the product obtained according to Example 1.

EXAMPLE 12

1.0 Gram of diphenylmethyl - 3 - hydroxymethyl - 7β - [N' - tert. - butyloxycarbonyl-D - (α) - phenylglycylamino] - ceph - 3 - em - 4 - oate (m.p. 121°C) recrystallised from toluene and 10.0 g of benzoic anhydride are dissolved in 20 ml of absolute dimethylsulphoxide. The colourless solution is left to stand in the dark for 5 hours at room temperature. The light brown reaction mixture is then evaporated to dryness in a high vacuum. The oily residue is taken up in 50 ml of methylene chloride and extracted with 2×70 ml of 5% sec. potassium phosphate solution and 70 ml of saturated sodium chloride solution. The organic extract is dried with anhydrous magnesium sulphate and evaporated to dryness *in vacuo*. Excess benzoic anhydride is separated from the residue by digesting with 2×200 ml of petroleum ether. The now solid, yellow residue is poured onto a column of silica gel (50 g; MERCK puriss. with 10% water). Elution is carried out firstly with methylene chloride-toluene (1:1); fractions of 50 ml each are collected. Fractions 1—3 contains impurities, which are discarded. Diphenylmethyl - 3 - formyl - 7β - [N' - tert. - butyloxycarbonyl - D - (α) - phenylglycylamino] - ceph - 3 - em - 4 - oate (552 mg), which is pure according to thin-layer chromatography, is isolated from fractions 8—11 (elution with methylene chloride). The product crystallises from diethyl ether in the form of colourless needles (m.p. 179—181°C, with decomp.).

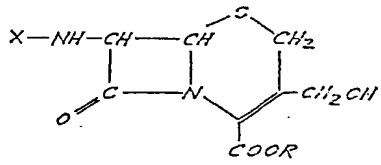
WHAT WE CLAIM IS:—

1. A process for the manufacture of a 7 - amino - cephalosporanic acid derivative of the formula I



(I)

in which X represents a hydrogen atom or an acyl residue and R_1 represents a hydrogen atom, a salt-forming cation or OR_1 represents a substituted methyl ester group that can be split off by solvolysis, enzymolysis, photolysis or reduction, wherein a compound of the formula II



(II)

in which X has the meaning given above and OR stands for a substituted methyl ester group that can be split off by solvolysis, enzymolysis, photolysis or reduction is oxidised with an aliphatic sulphoxide in the presence

of an anhydride of a carboxylic acid and, if desired, the resulting compound is converted into a salt or a resulting salt is converted into another salt.

2. A process as claimed in claim 1, wherein 1, wherein a compound of the formula II is used as starting material, in which OR is a sterically hindered, substituted methyl ester group.

3. A process as claimed in claim 1, wherein a compound of the formula II is used as starting material, in which OR is a methyl ester group that is substituted by at least one unsubstituted or substituted monocyclic or bicyclic aryl or aroyl radical.

4. A process as claimed in claim 1, wherein a compound of the formula II is used as starting material, in which OR is a methyl ester group that is substituted by at least one unsubstituted or substituted phenyl radical.

5. A process as claimed in claim 1, wherein a compound of the formula II is used as starting material, in which OR is an unsubstituted or substituted benzhydryl ester group.

6. A process as claimed in claim 1, wherein a compound of the formula II is used as starting material, in which OR is a benzhydryl ester group.

7. A process as claimed in any of claims 1 to 6, wherein a compound of the formula II is used as starting material, in which X is the radical of a carboxylic acid.

8. A process as claimed in any of claims 1 to 6, wherein a compound of the formula II is used as starting material, in which X is the radical of a thiocarboxylic acid.

9. A process as claimed in any one of claims 1 to 6, wherein a compound of the formula II is used as starting material, in which X is a radical derived from carbonic acid.

10. A process as claimed in any one of claims 1 to 9, wherein the oxidation is carried out with a di-lower alkyl-sulphoxide.

11. A process as claimed in any one of claims 1 to 9, wherein the oxidation is carried out with dimethylsulphoxide.

12. A process as claimed in any one of claims 1 to 11, wherein the oxidation is carried out in the presence of a lower alkanecarboxylic acid anhydride.

13. A process as claimed in any one of claims 1 to 11, wherein the oxidation is carried out in the presence of acetic anhydride.

14. A process as claimed in any one of claims 1 to 13, wherein the oxidation is carried out at a temperature in the range of from −50 to +70°C.

15. A process as claimed in any one of claims 1 to 14, wherein the ester group is split off by means of an acid.

16. A process as claimed in any one of claims 1 to 14, wherein the ester group is split off with trifluoracetic acid.

17. A process as claimed in any one of claims 1 to 16, wherein 3 - formyl - 7 - phenylacetylamino - ceph - 3 - em - 4 - carboxylic acid or a salt or substituted methyl ester thereof, is manufactured.

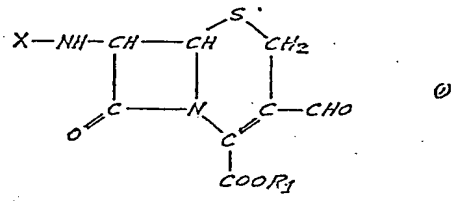
18. A process as claimed in any one of claims 1 to 16, wherein 3 - formyl - 7 - thienyl(2) - acetylamino - ceph - 3 - em-4 - carboxylic acid or a salt or substituted methyl ester thereof, is manufactured.

19. A process as claimed in any one of claims 1 to 16, wherein 3 - formyl - 7 - [N' - D - (α) - phenylglycylamino] - ceph-3 - em - 4 - carboxylic acid or a derivative having a protected amino group, or a salt or substituted methyl ester thereof, is manufactured.

20. A process as claimed in any one of claims 1 to 16, wherein 3 - formyl - 7 - [N' - tert.butyloxycarbonyl - D - (α) - phenylglycylamino] - ceph - 3 -em - 4 - carboxylic acid or a salt or substituted methyl ester thereof, is manufactured.

21. A process for the manufacture of a 7 - amino - cephalosporanic acid derivative of the formula I as defined in claim 1 conducted substantially as described in any one of the Examples herein.

22. A compound of the formula I



wherein X represents a hydrogen atom or an acyl radical and R_1 represents a hydrogen atom, a salt-forming cation or OR_1 represents a substituted methyl ester group that can be split off by solvolysis, enzymolysis, photolysis or reduction, whenever manufactured by a process as claimed in claim 1.

23. A compound of the formula I according to claim 22, wherein X has the meaning given therein and OR_1 represents a methyl ester group that is substituted by at least one unsubstituted or substituted monocyclic or bicyclic aryl or aroyl radical, whenever manufactured by a process as claimed in claim 1.

24. A compound of the formula I according to claim 22, wherein X has the meaning given therein and OR is a substituted methyl ester group that is substituted by at least one unsubstituted or substituted phenyl radical, whenever manufactured by a process as claimed in claim 1.

25. A compound of the formula I according to claim 22, wherein X has the meaning given therein and OR_1 represents an unsubstituted or substituted benzhydryl ester group, whenever manufactured by a process as claimed in claim 1.

26. A compound of the formula I according to claim 22, wherein X has the meaning given therein and OR_1 is a benzhydryl ester group, whenever manufactured by a process as claimed in claim 1.

27. A compound of the formula I according to claim 22, wherein X has the meaning given therein and R_1 stands for a hydrogen atom, whenever manufactured by a process as claimed in claim 1.

28. A compound of the formula I according to claim 22, wherein X has the meaning given therein and R_1 stands for an alkali or alkaline earth metal or ammonium ion, whenever manufactured by a process as claimed in claim 1.

29. 3 - Formyl - 7 - phenylacetylamino-ceph - 3 - em - 4 - carboxylic acid or a salt or substituted methyl ester thereof, whenever manufactured by a process as claimed in claim 1.

30. 3 - Formyl - 7 - [N' - tert.butyloxycarbonyl - D - (α) - phenylglycylamino]-ceph - 3 - em - 4 - carboxylic acid or a salt or substituted methyl ester thereof, whenever manufactured by a process as claimed in claim 1.

31. 3 - Formyl - 7 - [N' - D - (α) - phenylglycylamino] - ceph - 3 - em - 4 - carboxylic acid or a derivative having a protected amino group, or a salt or substituted methyl ester thereof, whenever manufactured by a process as claimed in claim 1.

32. 3 - Formyl - 7 - thienyl(2) - acetylamino - ceph - 3 - em - 4 - carboxylic acid or a salt or substituted methyl ester thereof whenever manufactured by a process as claimed in claim 1.

33. A compound of the formula I as claimed in claim 22, and which is prepared by a process as described in any one of the Examples herein.

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